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21 ST CENTURY PATHOLOGY

21st Century Pathology

Review Article

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Unusual Manifestations of Orbital Langerhans Cell Histiocytosis: Conjunctival Hyperemia and Ocular Hypertonia

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Received: 20 February 2022; **Accepted:** 26 February 2022; **Published:** 28 February 2022

Abstract

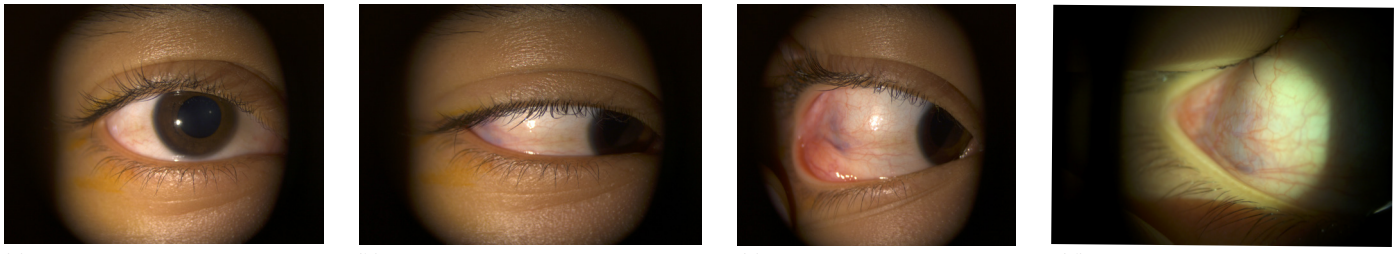
Langerhans cell histiocytosis (LCH) is a rare disease defined by the pathological proliferation of the monocyte-macrophage lineage and dendritic cells. Orbital involvement typically manifests as a solitary lesion that carries a favorable prognosis. We describe the clinical and histological profile of an orbital LCH case. The patient exhibited unifocal unisystem disease. Typical histologic features included numerous histiocytes with varying degrees of giant cell formation and scattered eosinophilic granulocytes. The presence of Langerhans cells was confirmed by CD1a and CD68 immunohistochemistry. We reviewed the different ophthalmic manifestations of LCH and treatment strategies. As LCH may solely involve the orbit, treatment is based on the degree of organ involvement. LCH should be included in the differential diagnosis of tumors of the ocular adnexa, especially in young children.

Introduction

Langerhans Cell Histiocytosis (LCH) is a rare disease defined by the pathological proliferation of the monocyte-macrophage lineage and dendritic cells. It has long been referred to as histiocytosis X, a term covering Eosinophilic granuloma, Hand – Schuller – Christian disease, and Letterer –Siwe disease [1]. It can affect one or several organs. The orbital location of LCH represents 1% of orbital tumors [2]. It is often a uni-focal uni-system disease but can evolve to a multi-system disease. The symptomatology is a large mosaic, ranging from discrete to patent. The diagnosis is based on histopathological analysis. The extension assessment is an important step in medical care, it conditions therapeutic management and prognosis. Even if the therapeutic arsenal is varied, there is no standardized protocol. Many authors have reported successful outcomes after biopsy, curettage, and intralesional corticosteroid injection [3-6]. The present study aims to describe the atypical clinical presentation of LCH of the orbit and the different therapeutic strategies.

Clinical Observation

A 15-year-old child, with no particular medical history, was admitted to the emergency room for acute redness and pain of the left eye. The ophthalmological examination found (Figure 1: A, B, C, D): A visual acuity of 20/20 in both eyes, intraocular pressure at 35 mmHg in the right eye and 30 mmHg in the left eye. On the right eye, we found discreet upper eyelid edema, conjunctival hyperemia localized in the external canthus, with a bluish appearance of the episclera. The rest of the examination found no other abnormality.



(a) (b) (c) (d)

Figure 1: Pictures of the right eye (a), in primary position (b), (c) sideway gaze showing conjunctival hyperemia localized in the external canthus with a bluish appearance of the episclera(x 6,3), (d) microscopic magnification (x 16).

An inflammatory blood test has been requested: hemogram, reticulocytes, blood smear, sedimentation rate, and C reactive protein, with no anomaly found. Orbito-cerebral CT scan was performed, which showed an extra conical nodular thickening centered on the lateral rectus of the right orbit, associated with sphenoid lysis (Figure 2).

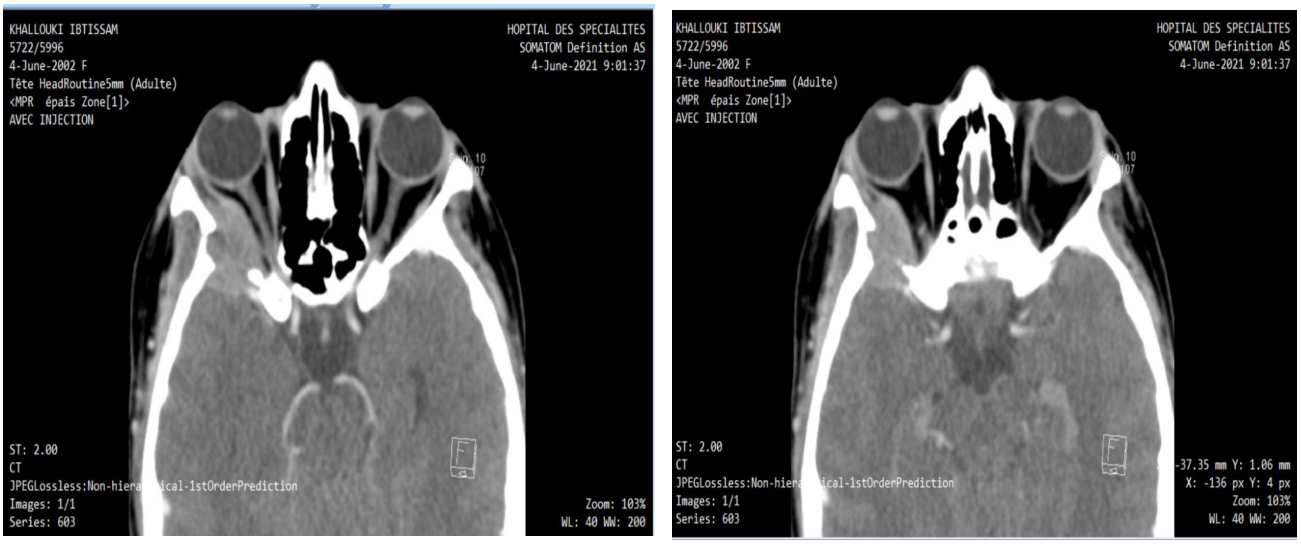
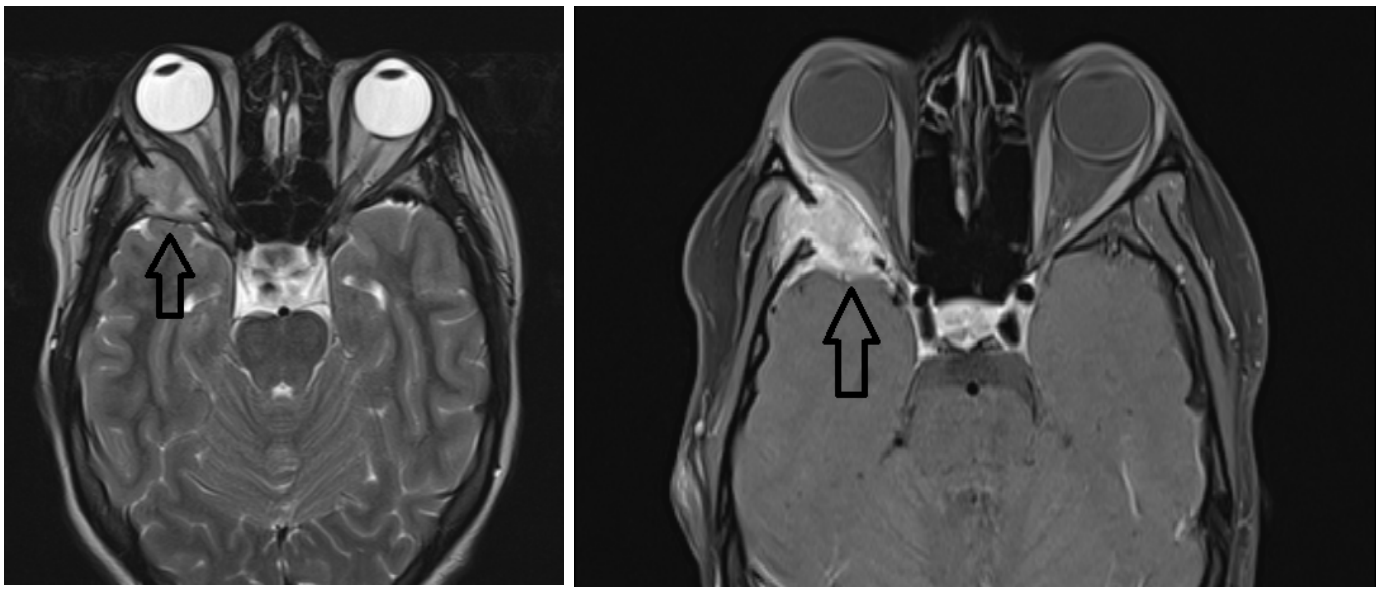


Figure 2: Cross-sections of orbital-cerebral CT showing an extra conical nodular thickening centred on the lateral rectus of the right orbit, associated with sphenoid lysis.

On MRI, the nodular lesion is hyposignal T2, isosignal T1, diffusion hypersignal, and intensely enhanced after injection. Pachymeningeal contrast on the endocranial side is related to reactive pachymeningitis (Figure3).



(a) (b)

Figure 3: Axial sections of brain MRI (arrow) showing a nodular lesion hyposignal T2 and isosignal T1 (a) and intensely enhanced after injection (b).

A treatment with beta-blocker eye drops and oral antalgic has been initiated. Afterward, a lateral orbitotomy biopsy was performed to make a definitive diagnosis. The morphological and immunohistochemical study showed positivity for anti CD1a and anti CD68 at the histiocytic level (Figure 4). The diagnosis was in favor of Langerhansian histiocytosis.

An extension assessment was conducted, finding no other localization of the LCH. The post-biopsy evolution was marked by the spontaneous normalization of the intraocular and the disappearance of pain. A monthly check-up was done by measuring tone, visual field, and papillary OCT.

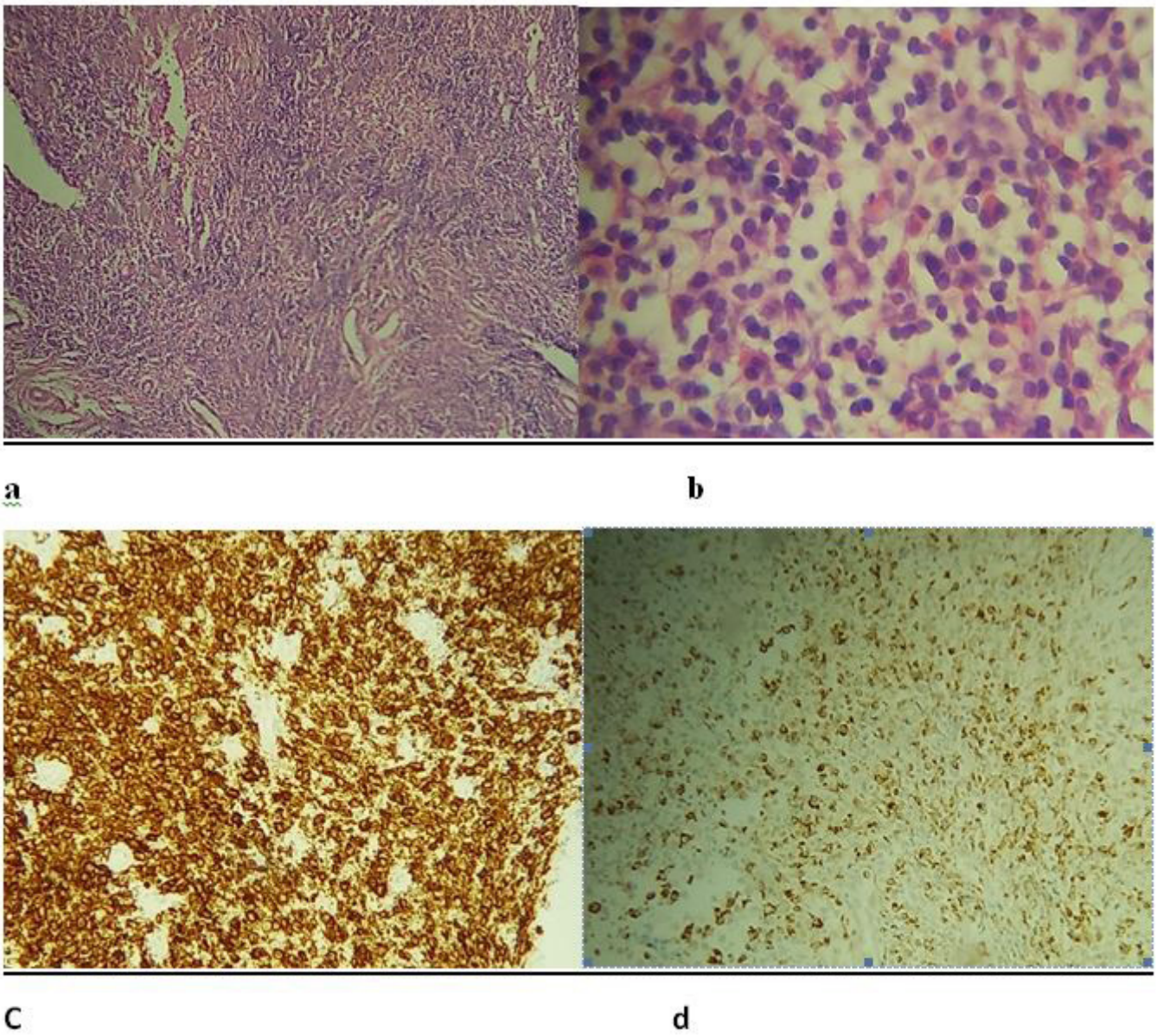


Figure 4: Microphotograph (hematoxylin and eosin stain, (a) 10 × and (b) 40×) showing numerous multinucleated giant cells, Langerhans cells with characteristic membrane grooving of the eosinophils, and showing diffuse immunoreactivity for CD1a protein and CD68 (c and d).

Discussion

Eosinophilic granuloma, Hand – Schuller – Christian disease, and Letterer- Siwe disease used to be referred to as Histiocytosis X. This was the case until the revision of the Histiocytic Society, defining Langerhans cell histiocytosis as the pathological proliferation of the monocyte-macrophage lineage and dendritic cells [1].

Langerhans histiocytosis boasts impressive flexibility in its affection, being able to affect an organ to multiple ones, and be uni or multifocal at their level. Its targets mainly comprise skin, bones, liver, spleen, lung, and central nervous system [2].

The most common ophthalmologic site is the rim of the frontal bone and the superior orbital roof, often in the form of isolated bone lysis associated with an endo-orbital mass [7]. Although the pathogenesis of Langerhans cell histiocytosis is not entirely understood [8], the frequency of its ophthalmic location may be explained by the presence of active hematopoietic marrow of the frontal bone's medullary space. With age, the frontal sinus dilates and the active hematopoietic zone is limited to the lateral orbital roof, which aligns with the very frequent superolateral roof location after the age of 8 years [9]. In some cases, such as our patient, hematopoietic activity in the sphenoid's greater wing may persist up to the second decade of life, which may explain that location in young adults [7, 9].

Statistically, orbital involvement represents 1-20% of unifocal-single system involvement, and globally constitutes 1% of orbital tumors [2]. Some European studies find an incidence rate varying between 4 and 6 / 1,000,000 children per year, with an incidence

of 9 to 15.3 / 1,000,000 per year for children under the age of 1, and 0.7 to 2 / 1,000,000 per year for those over 10 years old [10-13]. Although the diagnosis can be made at any age, two peaks of frequency stand out: between 1 and 4 years old, and in the third decade of life [14, 15].

From a clinical point of view, presentation depends on the tumor location and size. Anterior orbital location often results in ptosis and a mass or edema of the eyelid that can be mistaken for an infectious process. Posterior orbital location on the other hand may come with a proptosis, generally marked, along with diplopia, secondary to muscle infiltration or strabismus. Other rare locations have been reported, involving the eyelid, conjunctiva, caruncle, epibulbar nodule, choroid, optic chiasm, orbital apex, and cavernous sinus [13]. Visual acuity is usually preserved, with the exception of cases with papillary or macular edema.

As for imagery, a cerebral CT scan or MRI typically shows a characteristic aspect of bone lysis associated with a tissue mass in the periorbital space. Some cases without bone involvement have also been reported [16, 17].

The International Histiocytic Society has established criteria for Langerhans Cell Histiocytosis diagnosis. At least two items from the following are necessary: Positive staining for Adenosine triphosphate, S-100 protein, Alpha mannosidase, Peanut lectin binding. Definitive diagnosis requires the demonstration of Birbeck granules by electron microscopy or CD1a positivity [18]. Birbeck granules are rod-shaped, pentalaminar structures with vesicular end with an antigen presentation role. They are considered pathognomonic of LCH if present in 50-70% of the lesions [13].

Once the diagnosis of certainty is made, investigations to detect other possible locations are necessary. This is an important step, conditioning the treatment and the prognosis. Systemic evaluation should include complete hemogram, liver function test, coagulation profile, urine analysis and osmolarity, water deprivation test, chest X-ray, bone marrow analysis, a complete skeletal survey X-ray or PET scan, and imaging of abdomen and pelvis [19].

The differential diagnoses can be divided into clinical and histological. The clinical differential diagnoses for children are lymphoma, Ewing's sarcoma, leukemia, metastases, dermoid cyst, orbital cellulitis, acute dacryocystitis, or bone infection such as bone tuberculosis. For adults, differentials mainly consist of lacrimal gland tumors, meningiomas, dermoid cysts, and metastases [9]. The histological differential diagnosis is giant cell reparative granuloma, hemorrhagic cyst, cholesterol granuloma, Erdheim-Chester disease, giant cell aneurysm of bone, giant cell tumor, and the rare histiocytic and Langerhans cell sarcomas [13].

Concerning the prognosis, unifocal lesions present a better outcome than multisystemic lesions. Endocranial extension of an orbital LCH, considered a unifocal lesion [20], is correlated with a risk of developing diabetes insipidus [13].

Based on a systematic review, Bezdjian A, et al. (2015) created an algorithm to resume the diagnosis steps and guide the treatment (Figure 5) [21].

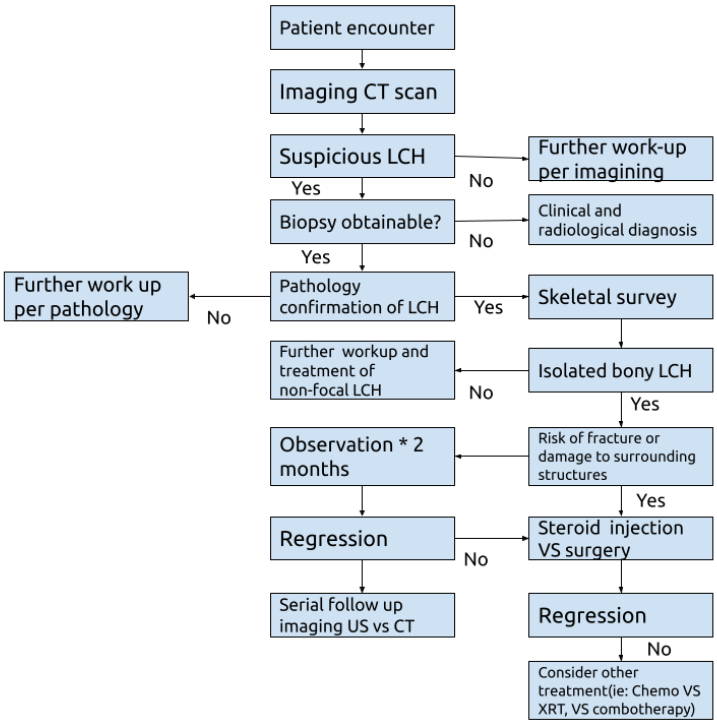


Figure 5: Treatment algorithm for the diagnosis and treatment of Langerhans cell histiocytosis (LCH) isolated bone lesions in the head and neck. CT, computed tomography; US, ultrasound.

A review of the literature shows the lack of standardized protocol for therapeutic management. Multiple factors must be taken into consideration: location of the lesion, uni or multifocality, whether it affects single or multiple organs, and recurrences. Many therapeutic approaches exist observation after biopsy, curettage, surgical excision, corticotherapy, radiotherapy, and chemotherapy.

For solitary orbital lesions, such as our case, biopsy and curettage are recommended by many authors. Spontaneous resolution following biopsy was reported by the likes of Smith JH, et al. (1999) and Glover AT, et al. (1987) [3, 4], while Rajendram J, et al. (2005) reported the resolution of the orbital LCH after curettage and intralesional steroids [5]. This mysterious outcome may be explained by the interruption of the pathological cascade through the modification of the microenvironment [6].

To prevent recurrences, intralesional corticotherapy post-excision at the dose of 125mg of methylprednisolone is recommended. It inhibits IL-1 and PGE2, and mediates osteolysis. Harris et al treated four out of seven patients with intralesional steroid post-excision and reported nil recurrence after a follow-up period of 6–24 months [6].

As for multifocal/multisystem disease or recurrences and in orbital lesions with dural involvement, chemotherapy constitutes a valid option [19, 22 and 23]. The LCH III protocol recommended systemic chemotherapy to prevent the development of "central nervous system" (CNS) complications, considering orbital disease as a CNS risk lesion [24]. Although there is no direct evidence proving the effect of chemotherapy in the prevention of progression to the central nervous system in the cases of unifocal orbital lesions [25].

Radiotherapy is usually proposed to treat recurrences [13]. Das et al documented regression without any recurrence at 4 years of follow-up in an 8-year-old girl with orbital LCH who received 1500 cGy in three fractions [23].

Last but not least, bone marrow transplantation and immunoglobulin therapy are reserved for uncontrolled disease recurrences and central nervous system involvement, respectively [26, 27]. Despite the Histiocyte Society presenting the latest treatment strategies, there is no standardized protocol for ophthalmological LCH. These trials are focused on multi-system disease and are not conducted by ophthalmologists [28, 29].

Conclusion

This case report highlights the importance of CT-scan in front of atypical inflammatory symptomatology with ocular hypertonia and the necessity to discuss tumor pathologies, especially in children.

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